Establishing and Prioritising Research Questions for the Treatment of Alopecia Areata: The Alopecia Areata Priority Setting Partnership

Summary

Background

Alopecia areata is a common hair loss disorder that results in patchy to complete hair loss. Many uncertainties exist around the most effective treatments for this condition.

Objectives

To identify uncertainties in alopecia areata management and treatment that are important to both service users (people with hair loss, carers and relatives) and healthcare professionals.

Methods

An alopecia areata priority setting partnership was established between patients, their carers and relatives, and healthcare professionals to identify the most important uncertainties in alopecia areata. The methodology of the James Lind Alliance was followed to ensure a balanced, inclusive and transparent process.

Results

In total 2747 treatment uncertainties were submitted by 912 participants, of which 1012 uncertainties relating to alopecia areata (and variants) were analyzed. Questions were combined into "indicative uncertainties" following a structured format. A series of ranking exercises further reduced this list to a top 25 that were taken to a final prioritization workshop where the top 10 priorities were agreed.

Conclusions

We present the top 10 research priorities for alopecia areata to guide researchers and funding bodies to support studies important to both patients and clinicians.

What's already known about the topic?
• Many uncertainties exist around the management and treatment of alopecia areata
What does the study add?
• We present the top 10 uncertainties in alopecia areata management and treatment that are important to service users (people with hair loss, their carers and relatives) and healthcare professionals • These prioritized research uncertainties can be used to guide researchers and funding bodies when deciding to invest in alopecia areata research studies

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Conflicts of interest: None declared.

Introduction

Alopecia areata (AA) is an autoimmune hair loss disorder with a reported lifetime risk of 1.7% [1] that typically presents as patchy areas of hair loss that may involve any scalp or body site [2]. The extent of hair loss can vary from a small coin-sized patch to complete scalp (*alopecia totalis*) or scalp and body hair loss (*alopecia universalis*). The skin itself shows no evidence of inflammation or scarring. Hair loss in AA is frequently associated with psychological distress and may present with symptoms of anxiety, depression or reduction in quality of life [3]. National guidelines reflect the many uncertainties that exist about optimal therapy in AA [4] with the latest Cochrane systematic review published in 2008 concluding "there is no good trial evidence that any treatment provides long-term benefit to patients with alopecia areata" [5].

The James Lind Alliance (JLA) is a project funded by the National Institute of Health Research (NIHR) with support from the Medical Research Council. The aim of the JLA is to provide infrastructure and support to patients and clinicians working together to identify the most important treatment uncertainties affecting their particular interest, in order to stimulate and prioritize future research in that area. The Priority Setting Partnership (PSP) presented here was proposed by the British Hair and Nail Society (BHNS) to address treatment uncertainties highlighted by systematic reviews, treatment guidelines and clinical experience for alopecia areata (including alopecia totalis / universalis). Working with the JLA and funded by the hair loss charity Alopecia UK, this PSP presents priorities for UK hair research in a bid to raise the profile of alopecia areata and to open research funding streams to address these important uncertainties.

The objectives of the Alopecia Areata PSP were (1) to work with people with AA, their partners / parents / carers and healthcare providers to identify uncertainties about AA treatment and management, (2) survey the research literature to identify uncertainties and research recommendations, (3) agree by consensus a prioritized list of those uncertainties, (4) translate these prioritized uncertainties into research questions that can be tested, (5) publicize the results of the PSP and process of obtaining them, and (6) take the results to

research commissioning bodies to be considered for funding. All identified uncertainties from this process will be added to the UK Database of Uncertainties about the Effects of Treatments (UK-DUETs) (www.library.nhs.uk/duets).

Initially, the plan was to explore uncertainties relating to AA as part of a larger "Hair Loss PSP" addressing all types of hair loss within the same process. However, analysis of the initial survey revealed that over half of the responses specifically related to alopecia areata (including *alopecia totalis* / *universalis*). Therefore, the Steering Group (SG) felt it was appropriate to separate the analysis at this point into two separate PSP processes that would run in parallel yet remain under supervision of the same SG membership. The rationale for this change was to prevent one condition dominating the process whilst maximizing identification of important uncertainties across all conditions studied. The Hair Loss PSP (excluding AA) is reported separately [ref to be inserted].

Methods

Following the principles and guidelines set by the JLA, the Alopecia Areata PSP adhered to a pre-determined protocol to ensure transparency and inclusivity of all parties within the process (www.jla.nihr.ac.uk/priority-setting-partnerships/hair-loss). The SG was established in March 2014 by the initial Co-champions (AEM, MH) according to the guidelines of the JLA to attempt to ensure balance of all stakeholder groups. The SG comprised four people with hair loss representing various patient support groups (JT, JC, KMM, JR), four Dermatologists (AEM, MH and 2 further individuals to represent the British Hair and Nail Society(PF) and the European Hair Research Society(AGM)), an Academic Psychologist, a registered Trichologist (CM) and a General Practitioner (GP)(RR). A JLA representative (SU) provided independent oversight of the PSP and chaired the SG to ensure that members adhered to the principles of the James Lind Alliance and that no individuals unduly influenced the process. All potential conflicts of interest were declared prospectively. The academic psychologist was unable to continue with the process but submissions represented this area well and a psychologist was invited to take part in the final workshop to ensure balance.

The five stages of the PSP process are outlined below and summarized in Figure 1.

Stage 1 – Identification and invitation of potential partners

Key stakeholders were identified through a process of consultation and peer knowledge, building on SG members' networks and existing JLA's affiliates. A broad range of stakeholder groups were approached and invited to become partners in the PSP process. In addition to the BHNS, JLA and Alopecia UK, the following partners engaged in the Alopecia Areata PSP: The British Association of Dermatologists (www.bad.org.uk), UK Dermatology Clinical Trials Network (UK-DCTN) (www.ukdctn.org), The Institute of Trichologists (www.trichologists.org.uk), British Dermatology Nursing Group (www.bdng.org.uk), Skin Conditions Campaign Scotland (www.skinconditionscampaignscotland.org), Alopecia Help and Advice (Scotland) (alopeciascotland.co.uk), Scottish Alopecia Support Group, My New Hair (www.mynewhair.org), British Association of Skin Camouflage (www.skin-camouflage.net), Changing Faces (www.changingfaces.org.uk), European Hair Research Society (www.ehrs.org) and 'Look Good, Feel Better' (www.lookgoodfeelbetter.co.uk).

Stage 2 – Invitation to submit uncertainties

Survey 1 took place from 8th September 2014 – 31st October 2014 and was open to any one residing in the UK The initial invitation to submit uncertainties involved an online survey (Survey Monkey™) accessed through the Alopecia UK website (www.alopeciaonline.org.uk). In addition, paper surveys were available on request and were also distributed at key events. Through engagement with the various partner organizations, local advertisement and via social media, a range of people with different hair loss conditions, their carers and relatives, and healthcare professions were targeted.

Uncertainties were invited by asking the following question: "Do you have questions about prevention, diagnosis or treatment of hair loss that need to be answered by research?". Participants were permitted to submit as many or as few questions as they wished, and these could relate to one or more hair loss conditions. The survey contained a participant information sheet to provide background to the process and survey text was designed to be easy to understand and provide all the relevant information for self-completion. Submitting the completed survey was considered as consent to participate in the PSP process and publish the (anonymized) uncertainties generated on UK-DUETs.

Stage 3 - Collation

The aim of this stage was to review all the submitted questions, exclude questions outside the remit of the PSP and generate "indicative uncertainties" (i.e. a collation of similar questions into one clear, understandable question presented in a standard format). Non-questions (e.g. statements or comments without questions within) and questions not directly relating to a hair loss disorder were excluded. Questions that could be resolved with reference to existing research evidence (so called "unknown knowns") were identified from existing sources of information, in particular systematic reviews, evidence based guidelines and prospective trial registries. Exclusion of questions or comments outside of the remit of the Alopecia Areata PSP were made by consensus within the SG. Uncertainties which were not adequately addressed by previous research were collated and will be entered into a hair loss section within UK DUETs (www.library.nhs.uk/duets).

Stage 4 – Ranking of treatment uncertainties

The aim of this stage was to generate a short-list of indicative uncertainties deemed by both people with AA and healthcare professionals to be important. To reduce the large number of indicative uncertainties generated in stage 3 to a reasonable number for ranking, an "interim list" was created using criteria agreed by the SG. These criteria were designed to identify which questions were asked most frequently, with weight given to questions asked by more than one person and questions asked by both patients and healthcare professionals independently. This process generated a list of 51 questions to go forward to the second survey.

The second online ranking survey was completed by previous participants, by invitation, to further refine the interim list into a short-list of 25 uncertainties to take to the final workshop. 500 participants from the initial survey had provided contact details and were invited to participate in the interim ranking. 87 participants (17.4%) returned responses for the second survey. Participants were invited to choose up to ten uncertainties from the interim list that they considered to be most important but were not asked to prioritise them. The responses obtained were used to rank the uncertainties by number of votes. The priorities of the different groups of responders were listed separately and compared.

Stage 5- Final workshop

The final workshop took place on 6th November 2015 at Willan House in London. The aim of this stage was to prioritize, through consensus, the most popular uncertainties relating to the

management of AA from the 25 uncertainties generated by the interim process. Attendance at the final workshops was designed to represent a balanced distribution of interested parties and ensuring a good representation from patients (7/19) and healthcare professionals (5 Dermatologists, 3 Trichologists, 3 GPs and a Psychologist). Those attending the priority setting workshop were asked to complete a declaration of interests, including disclosure of relationships with for-profit organizations. The final workshop was facilitated by three independent JLA facilitators to ensure fairness, transparency and accountability and to ensure no unfair influence by any individual. Using nominal group technique, 100% consensus was achieved through ranking and plenary sessions, eventually generating the top ten research priorities. During breakout groups, the uncertainties were ranked and allocated a numerical position. The 'scores', as the sum of the numerical positions in each break out group, were used to rank the questions for the whole group plenary discussion. 3 breakout sessions and 3 whole group plenaries were required to achieve consensus.

Results

The initial survey was completed by 912 participants generating 2747 responses, 83% from patients, carers and relatives and 13% healthcare professionals (Figure 2). After removal of non-questions and those deemed "out of scope" (e.g. non-questions / statements / not directly relating to hair loss, etc.) 1823 uncertainties remained of which 1015 related to alopecia areata.

Twenty of the 1015 submitted uncertainties could be answered from available evidence and so were excluded. Indicative uncertainties were generated by combining similar questions and standardized using "PICO" (**P**opulation **I**ntervention **C**omparator **O**utcome) formatting. This process generated an interim list of 170 uncertainties that was further reduced by ranking questions based on the number of submissions, with priority given to those questions posed by both patients and healthcare professionals. The top 51 uncertainties were taken forward to the second ranking survey that ran from 22nd September 2015 to 4th October 2015. The top 25 uncertainties were taken to the final workshop on 6th November 2015 to select the "Top 10" research uncertainties by consensus (Table 1).

Conclusion

Here we present an overview of this PSP that has demonstrated a number of uncertainties relating to the management and treatment of AA. By adhering to the JLA ethos of inclusivity

and transparency, and using a combination of online surveys and face-to-face workshops, we can feel confident that the outcomes generated here accurately reflects the consensus view of both service users (people with AA, carers and relatives) and healthcare professionals in determining future priorities for AA research.

Feedback from participants in the final workshop revealed that the opportunity to discuss the questions allowed different viewpoints to be aired, identified positions that they had not previously considered and gave rise to a more balanced appraisal of the priorities. Thus, the final top 10 did not exactly reflect the ranking (performed independently) from the second survey. Discussion on position of ranking was frequently influenced by the other questions presented, with certain questions relegated in priority if they were deemed to be covered by other uncertainties more highly ranked in the process. Although deliverability of the research was considered in appraising each question, it was acknowledged that the questions broadly represented a theme for research that would require refinement before being developed into a completed research question. A workshop has been planned to further progress these research uncertainties to fully formed research questions and to develop vignettes.

Interestingly, a significant proportion of the originally submitted questions did not represent an uncertainty at all, but reflected a lack of information around treatment options and service provision. Recurring themes included availability of services, treatment strategies, wig provision and the low priority given to hair loss in the NHS. Striking was the frequency of comments relating to experiences of patients accessing medical services, particularly seeing GPs, with many describing a perceived lack of knowledge, reluctance to refer and in some cases a lack of compassion when dealing with their distressing problem. Thus, a greater awareness and education of GPs / healthcare professionals around hair loss was suggested to highlight and address the (openly acknowledged) inadequate dermatology training currently received in the UK by many medical students and GP trainees in the field of hair loss.

Some problems were encountered during the process mainly around data handling and the large number of uncertainties originally submitted (2747 questions). By necessity a “Data team” was set up to process these results. However, some inconsistency in taxonomy allocation to categorize questions occurred that may have been overcome by just one or two people only handling the results, although this would have significantly prolonged the process in time and costs. Another area of difficulty was around engagement of key

stakeholders. In general smaller and specialized organizations were keen to become partners in the process. However, some larger organizations were reluctant to commit to partnership but agreed to advertise the PSP to their members, whereas other groups refused to engage completely. These decisions appeared to relate to the inability of such large organizations to commit to these types of projects for which they are frequently approached to support. As the number of PSPs in all fields are likely to increase, with many groups anticipated to want engagement with similar stakeholders each time it was felt by the SG that the JLA should consider setting up a higher level agreement with the main stakeholder groups (particularly the Royal Colleges and Specialist Associations) to provide a minimum level of commitment for all future JLA-supported PSP processes.

We present an overview of the alopecia areata PSP process, including pitfalls encountered along the way. By presenting the top 10 uncertainties in AA identified as important by both patients and clinicians we hope to raise awareness of this disorder and influence research priorities in the future. These outcomes will be put forward to researchers and funding bodies with the ultimate aim of securing meaningful research funds to address these important issues.

Acknowledgments

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References

1 Safavi KH, Muller SA, Suman VJ *et al.* Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. *Mayo Clin Proc* 1995; **70**: 628-33.

2 Harries MJ, Sun J, Paus R *et al.* Management of alopecia areata. *BMJ* 2010; **341**: c3671.

3 Hunt N, McHale S. The psychological impact of alopecia. *BMJ* 2005; **331**: 951-3.

4 Messenger AG, McKillop J, Farrant P *et al.* British Association of Dermatologists' guidelines for the management of alopecia areata 2012. *Br J Dermatol* 2012; **166**: 916-26.

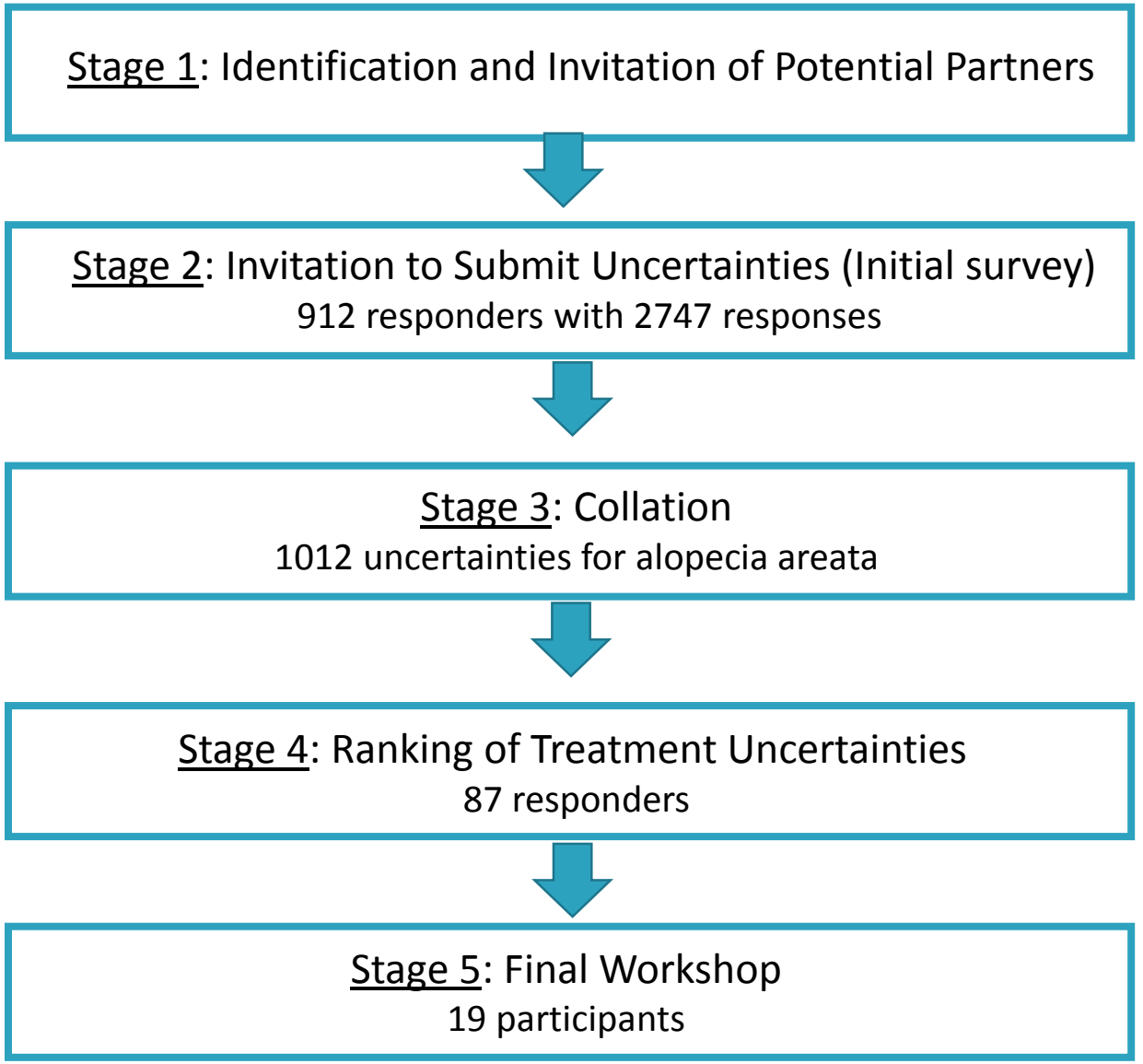
5 Delamere FM, Sladden MM, Dobbins HM *et al.* Interventions for alopecia areata. *Cochrane Database Syst Rev* 2008: CD004413.

Figure legends

Figure 1- Overview of the Alopecia Areata Priority Setting Partnership process

Figure 2- Division of participants of initial survey by category (n= 912)

Table 1- Top 10 research uncertainties for alopecia areata prioritized by consensus.


Stage 1: Identification and Invitation of Potential Partners
Stage 2: Invitation to Submit Uncertainties (Initial survey)
912 responders with 2747 responses
Stage 3: Collation
1012 uncertainties for alopecia areata
Stage 4: Ranking of Treatment Uncertainties
87 responders
Stage 5: Final Workshop
19 participants

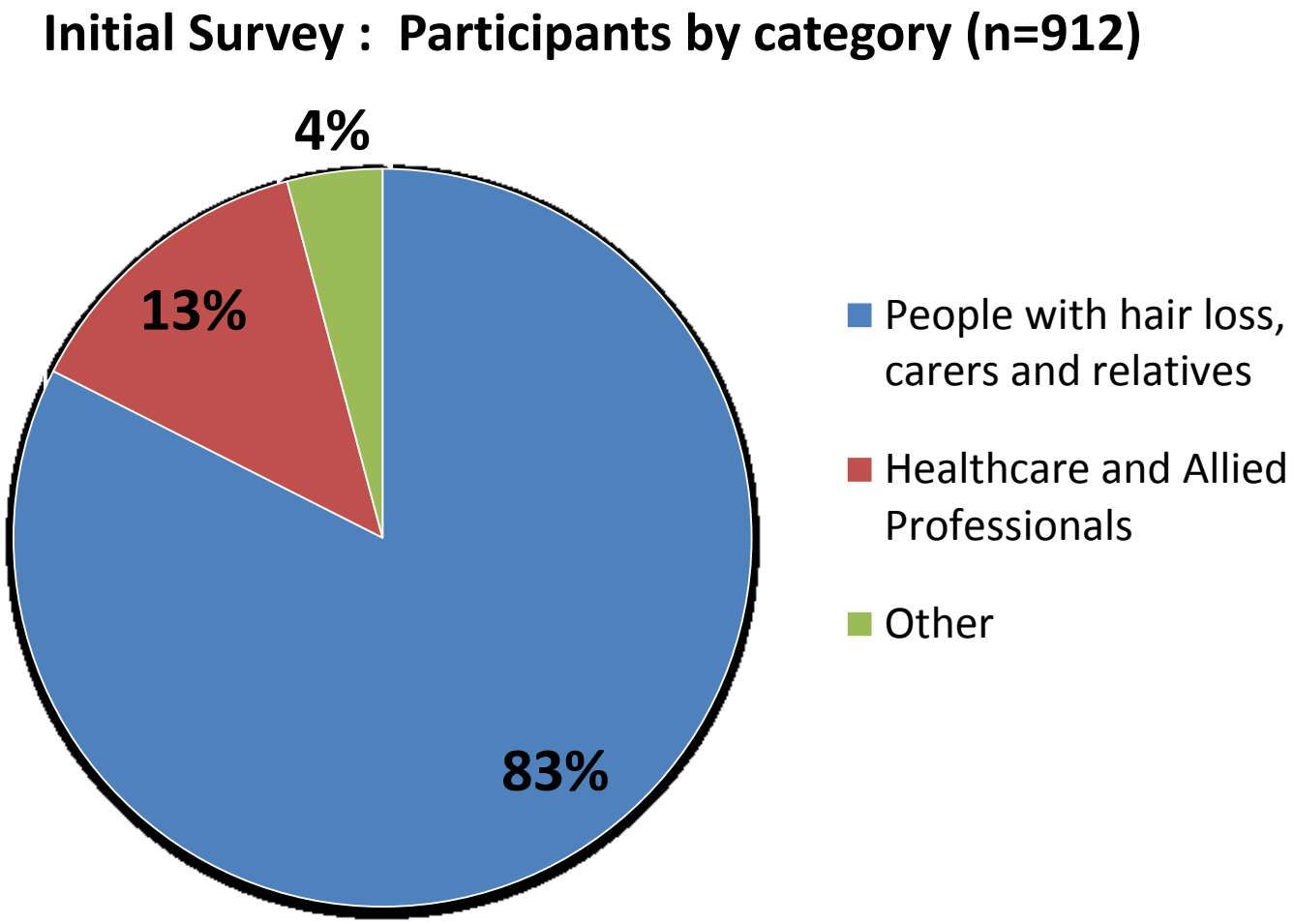


Figure 2- Division of participants in initial survey by category (n= 912)

Table 1- Top 10 research uncertainties for alopecia areata prioritized by consensus.

Rank	Uncertainty
1	What are the causes of alopecia areata? For example- medications, medical problems, lifestyle, vaccinations.
2	Are immunosuppressant therapies (for example- methotrexate, mycophenolate mofetil) better than placebo in the treatment of alopecia areata?
3	In alopecia areata, are biological therapies (including janus kinase (JAK) inhibitors and anti-cytokine therapies) more effective than placebo in causing hair regrowth?
4	Are psychological interventions helpful in alopecia areata?
5	Can progression of alopecia areata be prevented by early diagnosis and treatment?
6	Do certain foods, vitamins or nutritional supplements improve hair re-growth in alopecia areata?
7	What can be learnt about alopecia areata from other autoimmune conditions?
8	In whom does alopecia areata hair loss progress and why?
9	Do any treatments have a long-term therapeutic benefit in alopecia areata?
10	How effective are alternative therapies in alopecia areata?